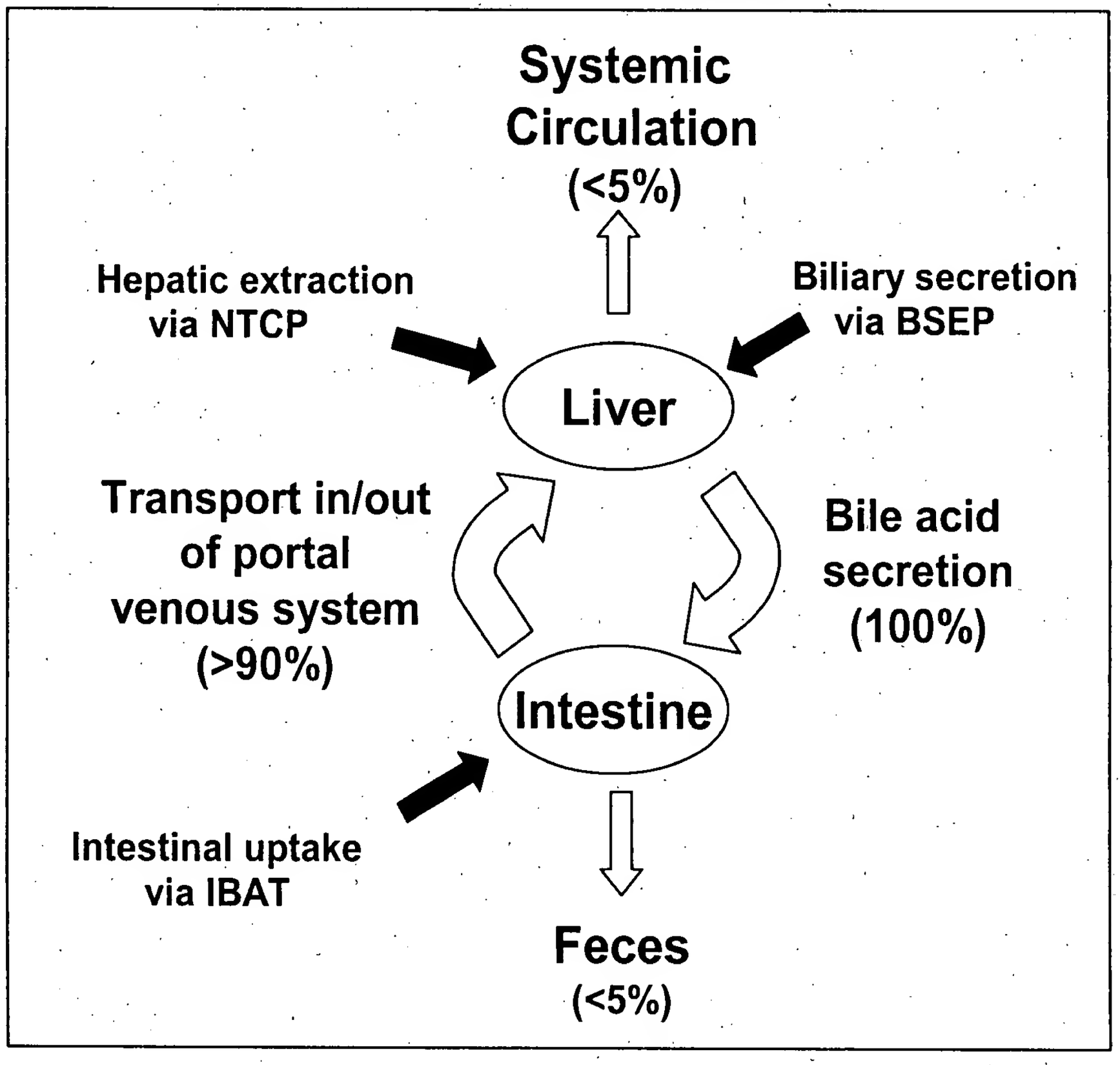
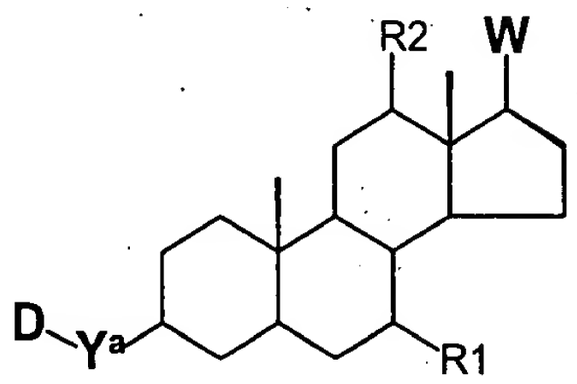
Figure 1

# The Enterohepatic Circulation with Key Transporter Proteins Mediating Bile Acid Circulation

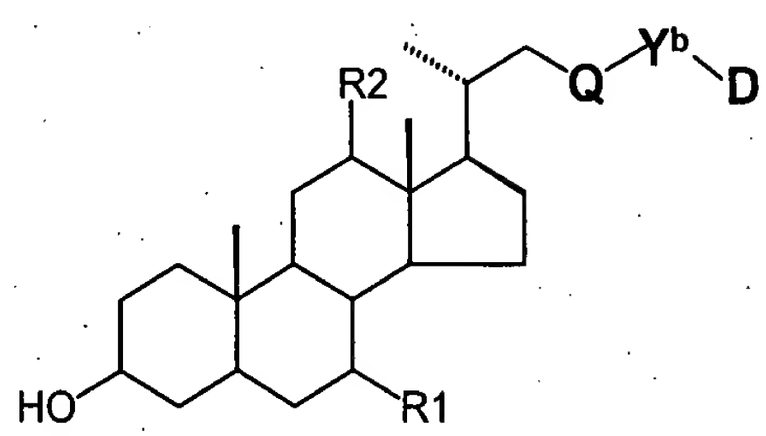


# Figure 2

## Bile Acid Prodrug Derivatives for Sustained Release of Drugs




(I-a)



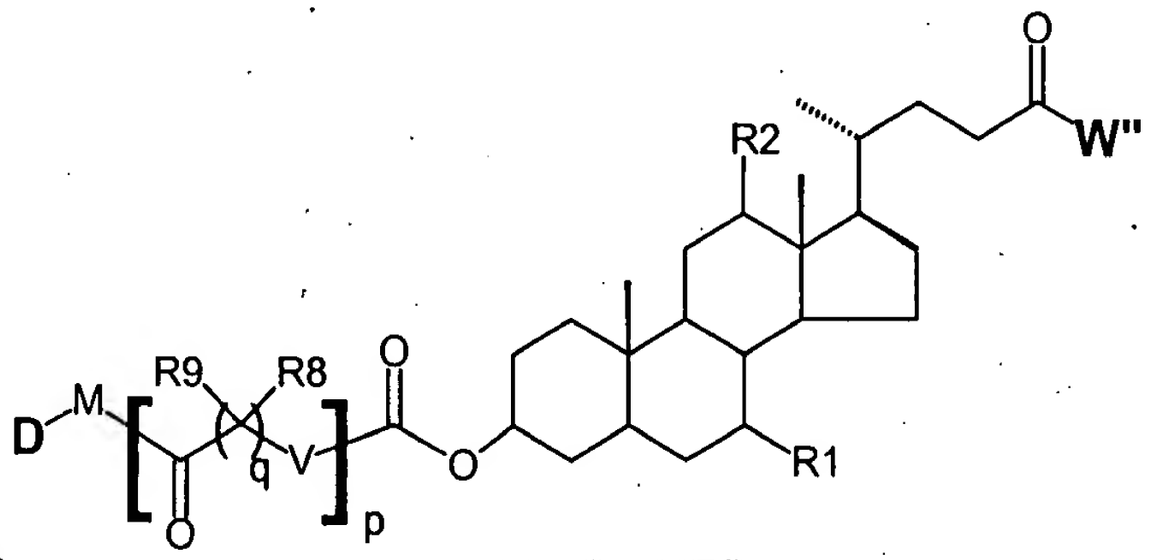

(I-b)

**Y**$^a$, **Y**$^b$ are cleavable linker groups
**D** is a drug moiety
**Q** is $CH_2$ or O
**W** is selected from the group consisting of -$CH(CH_3)$W' where W' is a substituted alkyl group containing a moiety which is negatively charged at physiological pH, which moiety is selected from the group consisting of -COOH, -$SO_3H$, -$SO_2H$, -P(O)($OR^6$)(OH), -OP(O)($OR^6$)(OH), -$OSO_3H$ and pharmaceutically acceptable salts thereof

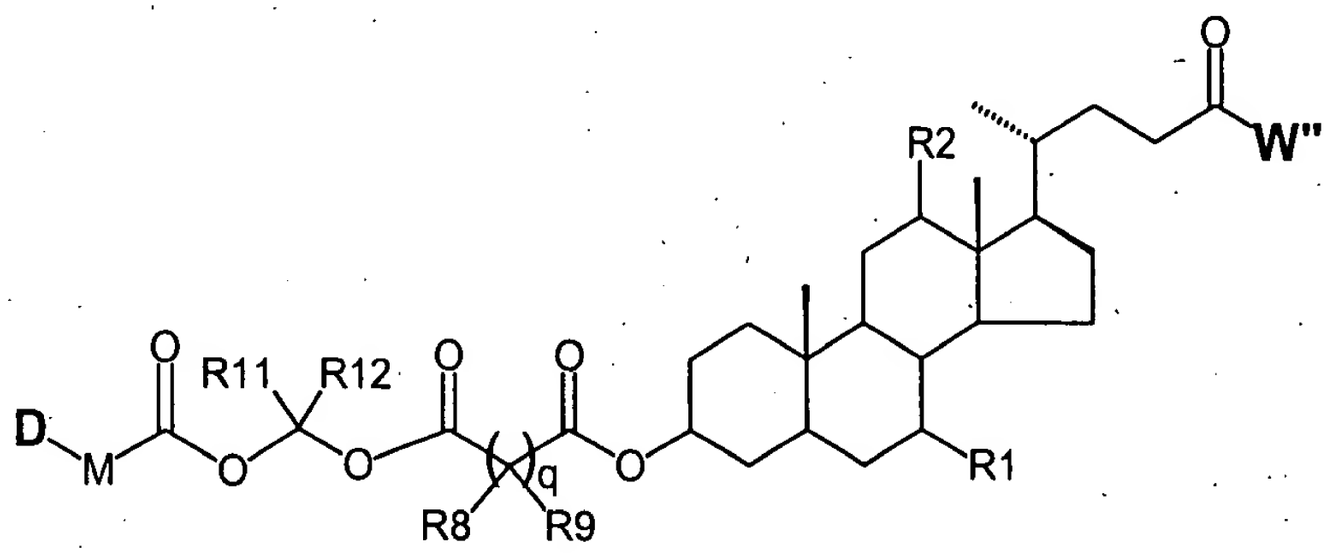
R1 = R2 = α-OH (from Cholate)
R1 = α-OH, R2 = H (from Chenodeoxycholate)
R1 = β-OH, R2 = H (from Ursodeoxycholate)
R1 = H, R2 = α-OH (from Deoxycholate)
R1 = β-OH, R2 = α-OH (from Ursocholate)
R1 = R2 = H (from Lithocholate)

# Figure 3- Generic Structures of Preferred Bile Acid C-3 Derivatives

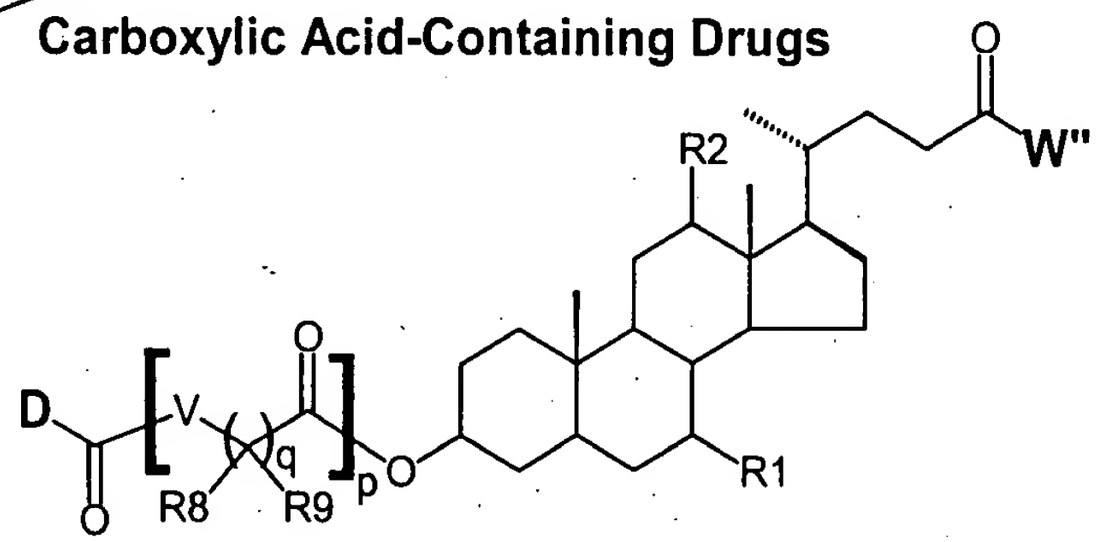
**Hydroxyl or 1° and 2° Amine-Containing Drugs**

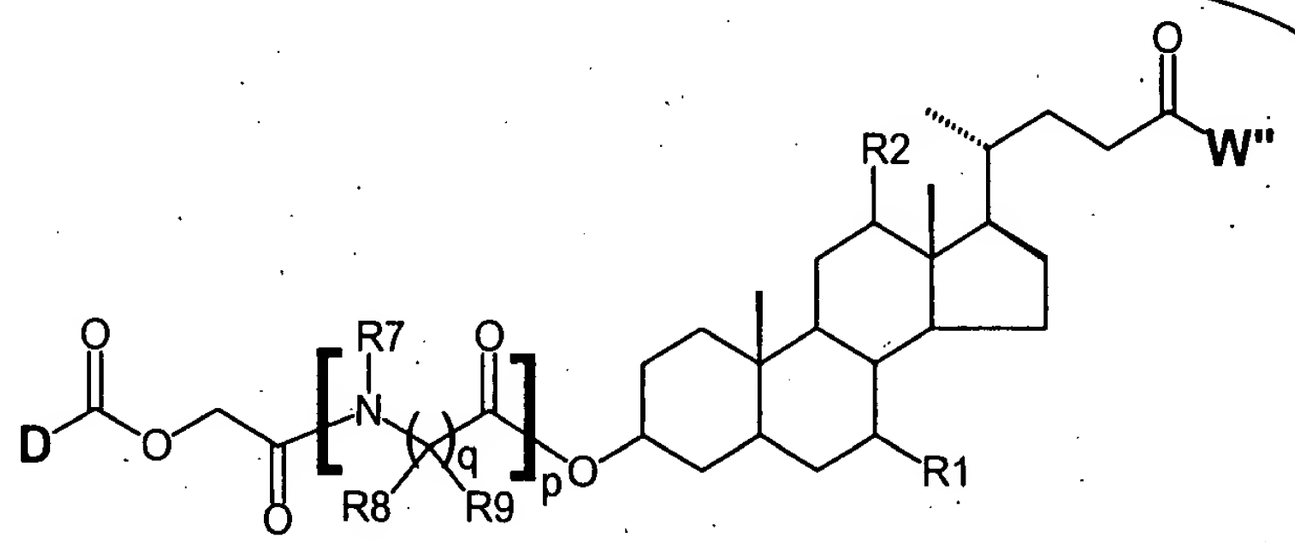


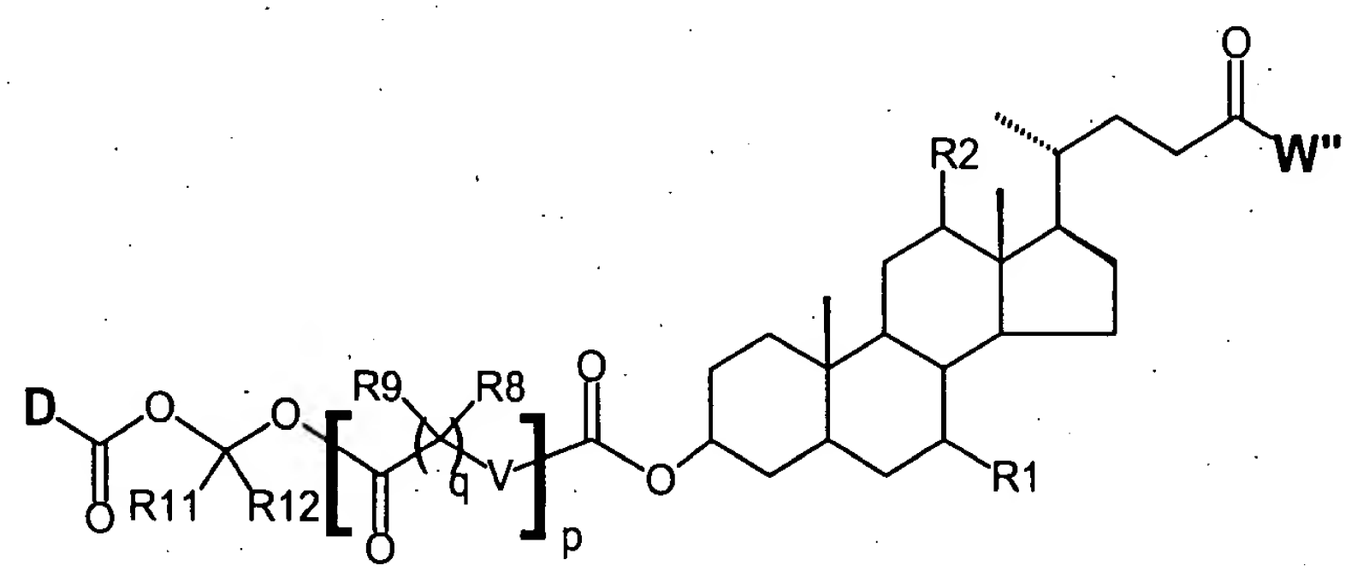

M= O , $NR^7$




**Carboxylic Acid-Containing Drugs**



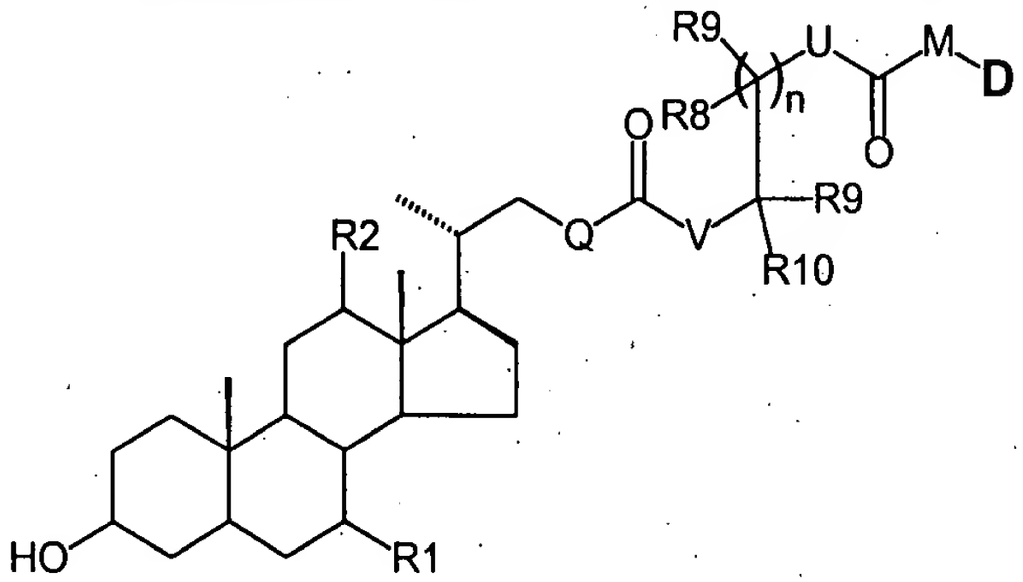



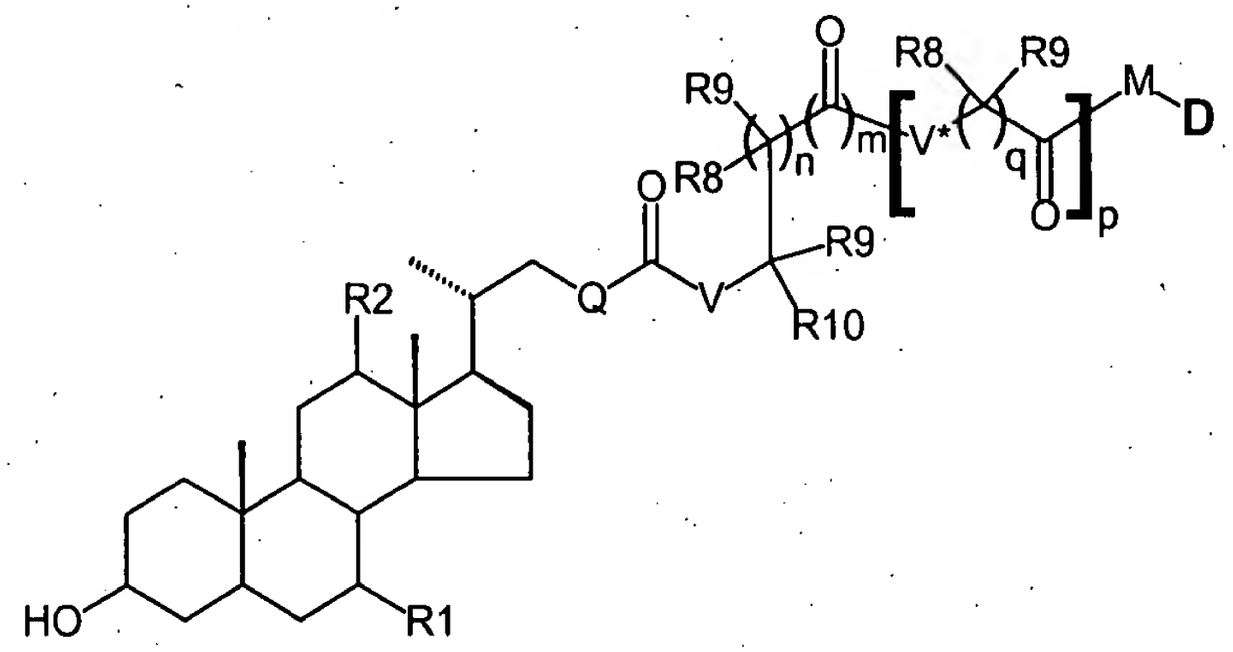



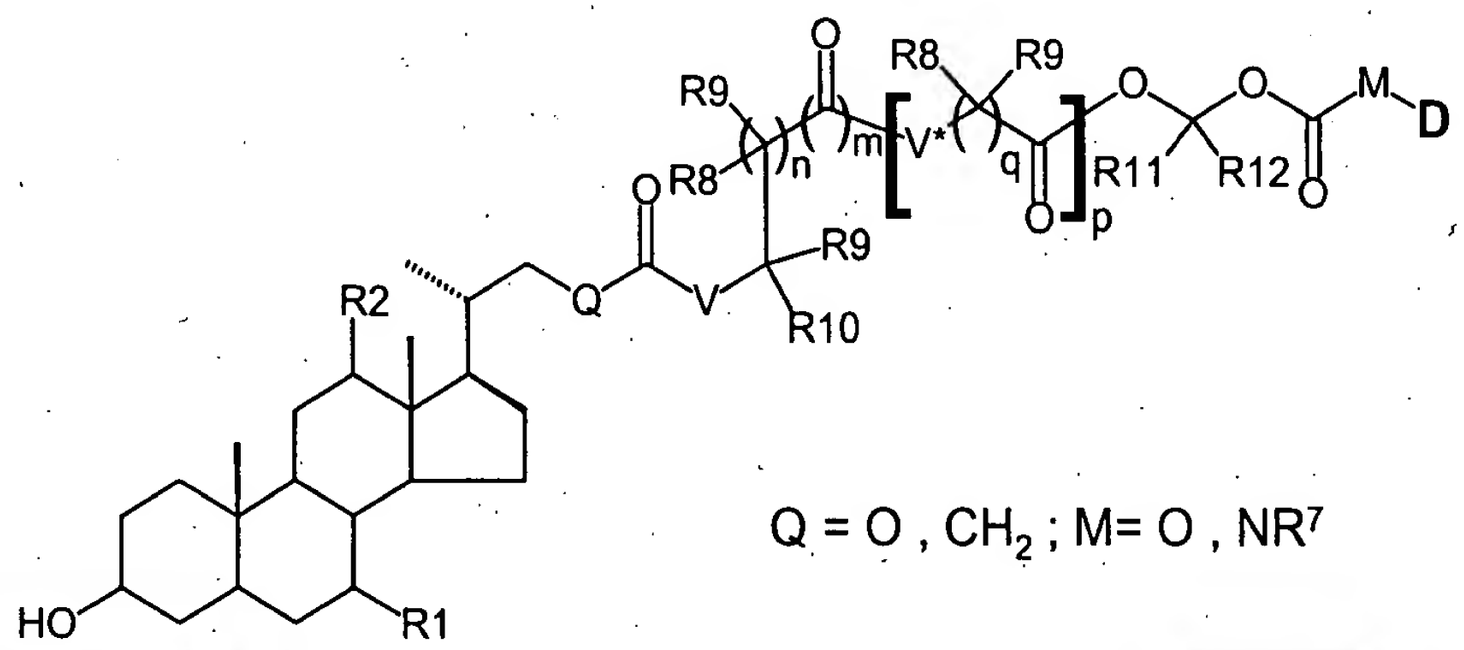

**W"** is OH , $NHCH_2CO_2H$, $NHCH_2CH_2SO_3H$ or pharmaceutically acceptable salts thereof

# Figure 4- Generic Structures of Preferred Bile Acid C-24 Derivatives

**Hydroxyl or 1° and 2° Amine-Containing Drugs**

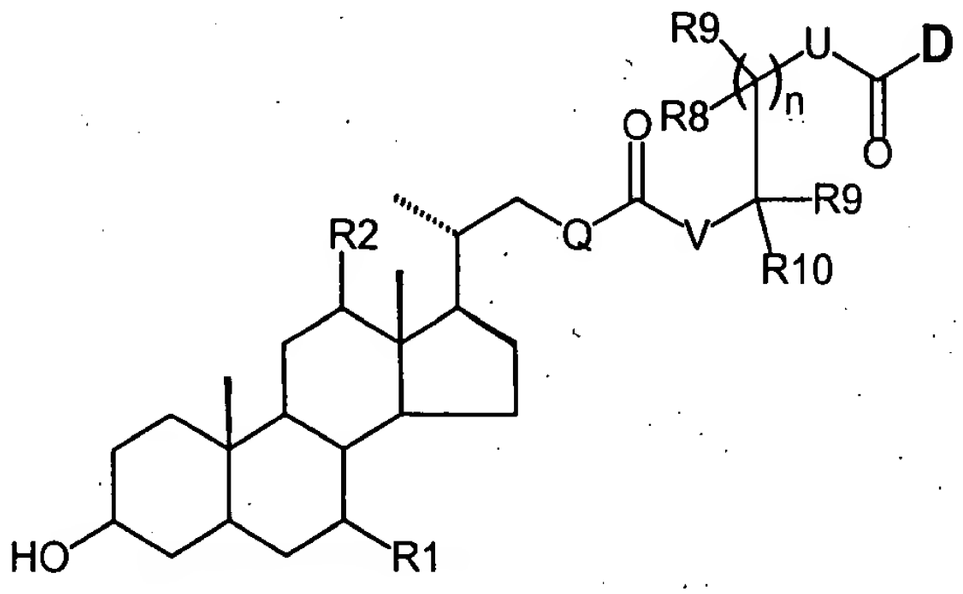


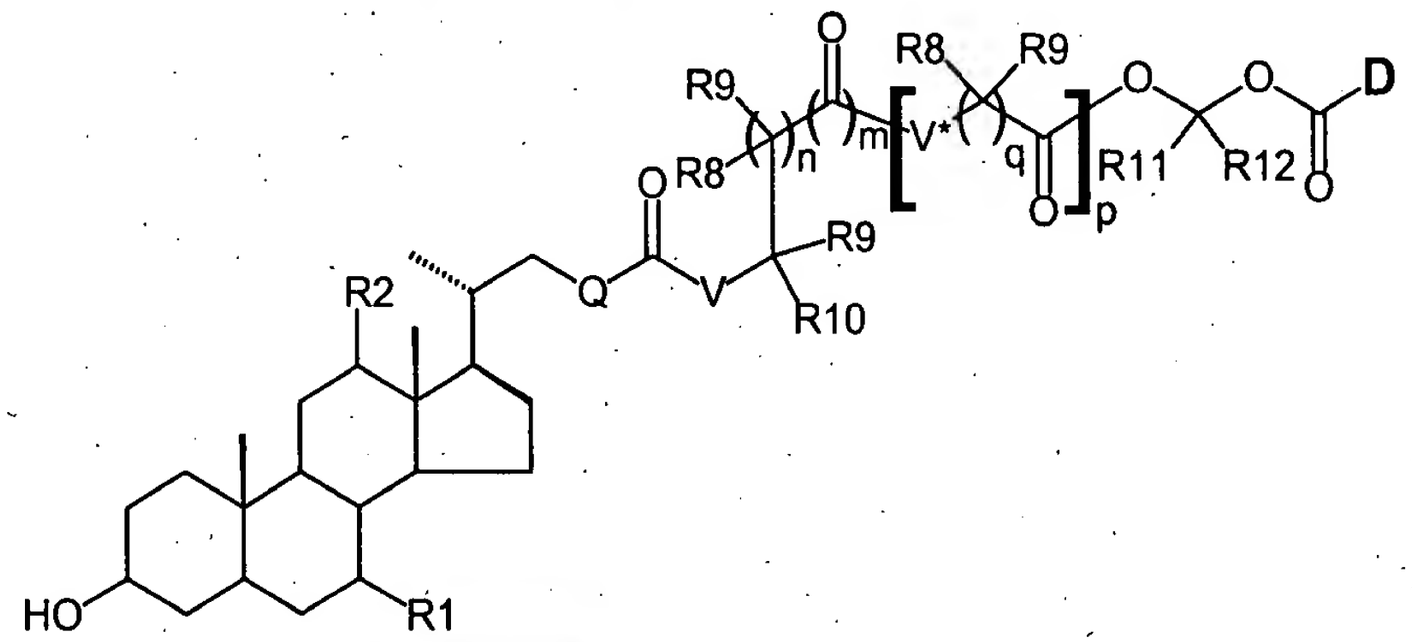




$Q = O , CH_2 ; M= O , NR^7$

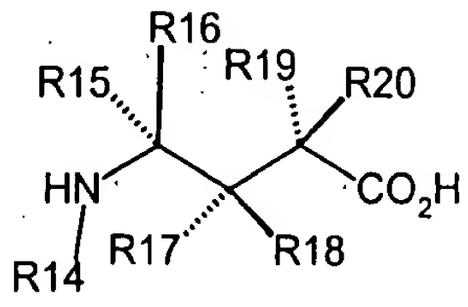
**Carboxylic Acid-Containing Drugs**



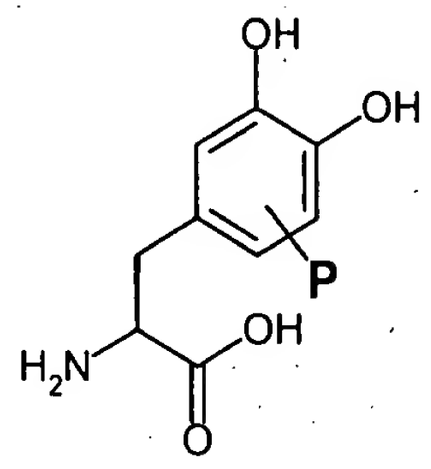



# Figure 5

## GABA Analog Derivatives and L-Dopa Derivatives




Generalized GABA Analog




Optionally Protected L-Dopa Analog

R14, R15, R16, R19 and R20 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl,aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl and substituted heteroarylalkyl;

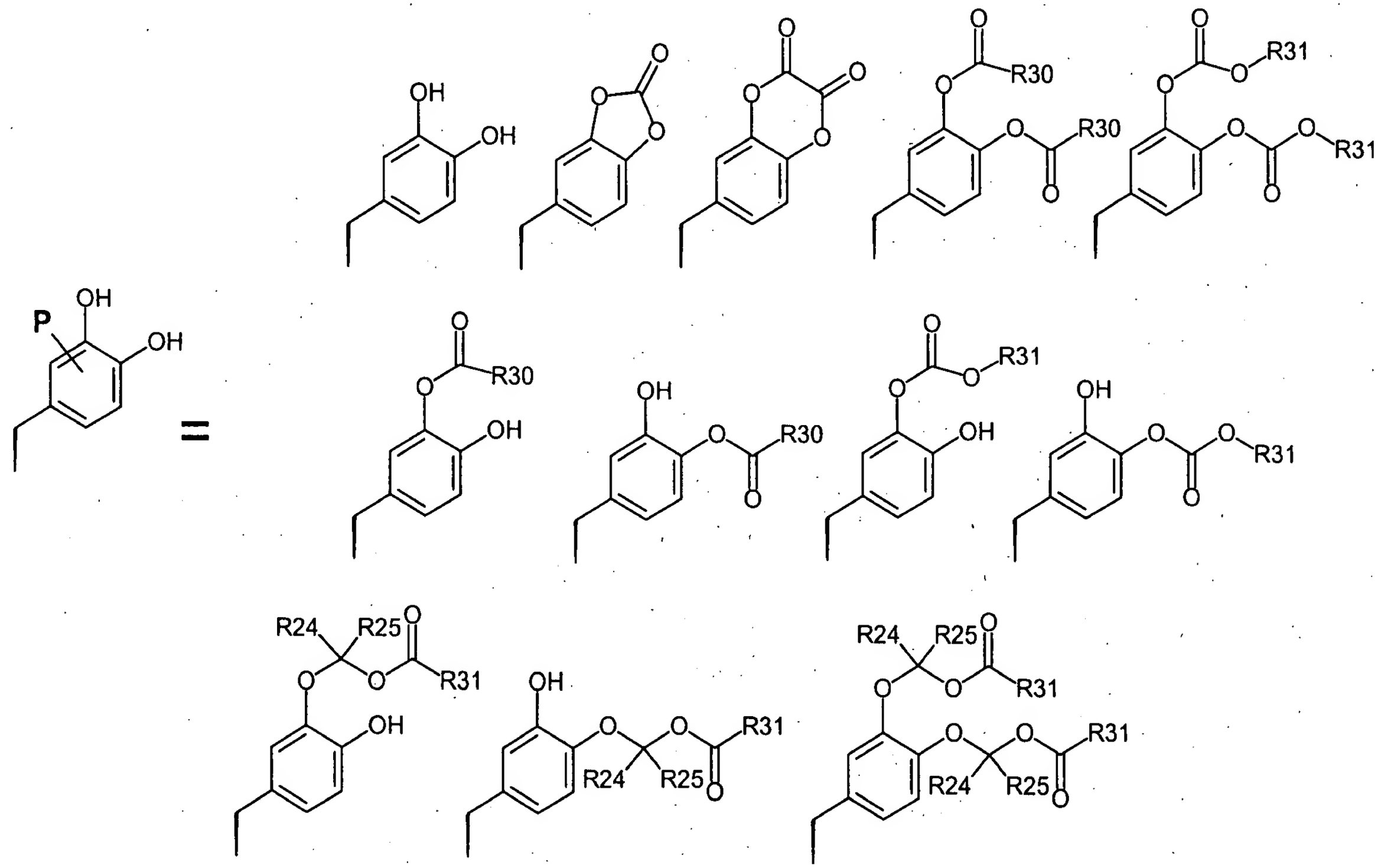
R17 and R18 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl,acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, heteroaryl, substituted het roaryl, heteroarylalkyl and substituted heteroarylalkyl or optionally, R17 and R18 together with the carbon atom to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl or bridged cycloalkyl ring;

P is a catechol protecting group (see Figure 6)

The GABA analog or L-Dopa analog is attached to the steroid nucleus in (I-a) or (I-b) either by replacement of one of the amino hydrogen atoms, or a hydrogen atom from one of the hydroxy groups of the catechol, or the hydroxyl group of the carboxyl moiety by a covalent bond to $Y^a$ or $Y^b$

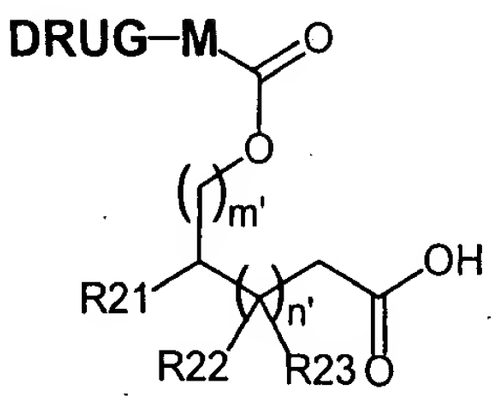
Figure 6:

# Catechol Protection Strategies Applicable for L-Dopa Bile Acid Conjugates

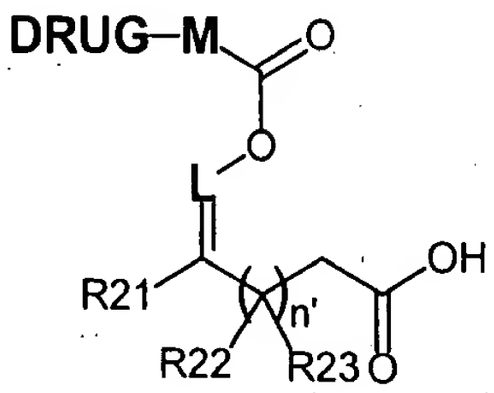



R30 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
R31 = alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
R24, R25 = hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl
or R24 and R25 together with the carbon to which they are attached form a cycloalkyl, substituted cycloalkyl, heterocycloalkyl or substituted heterocycloalkyl ring

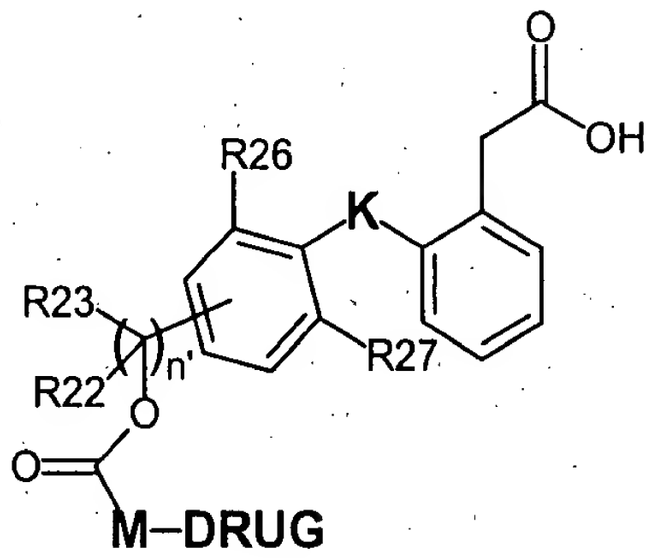
# Figure 7 - Prodrugs For Enterohepatic Circulation via Intestinal and Liver Anion Transporters



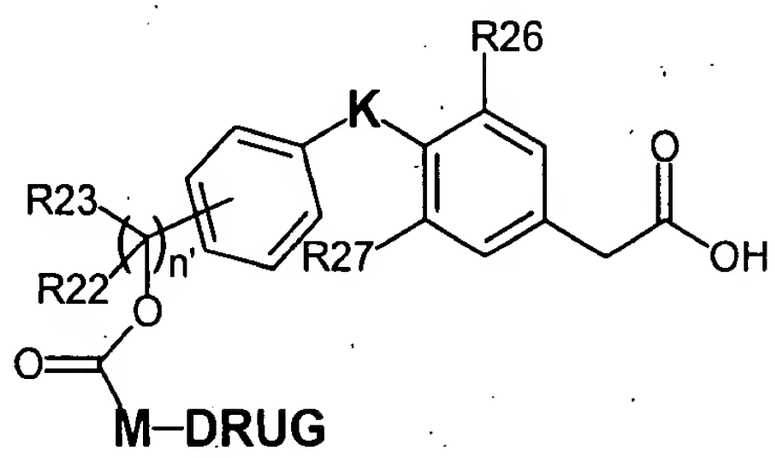

(XII)




(XIII)




(XIV)




(XV)

M = O , NR7 , CR8R9 m' is 0 to 6 ; n' is 0 to 6

L = CR8 , N

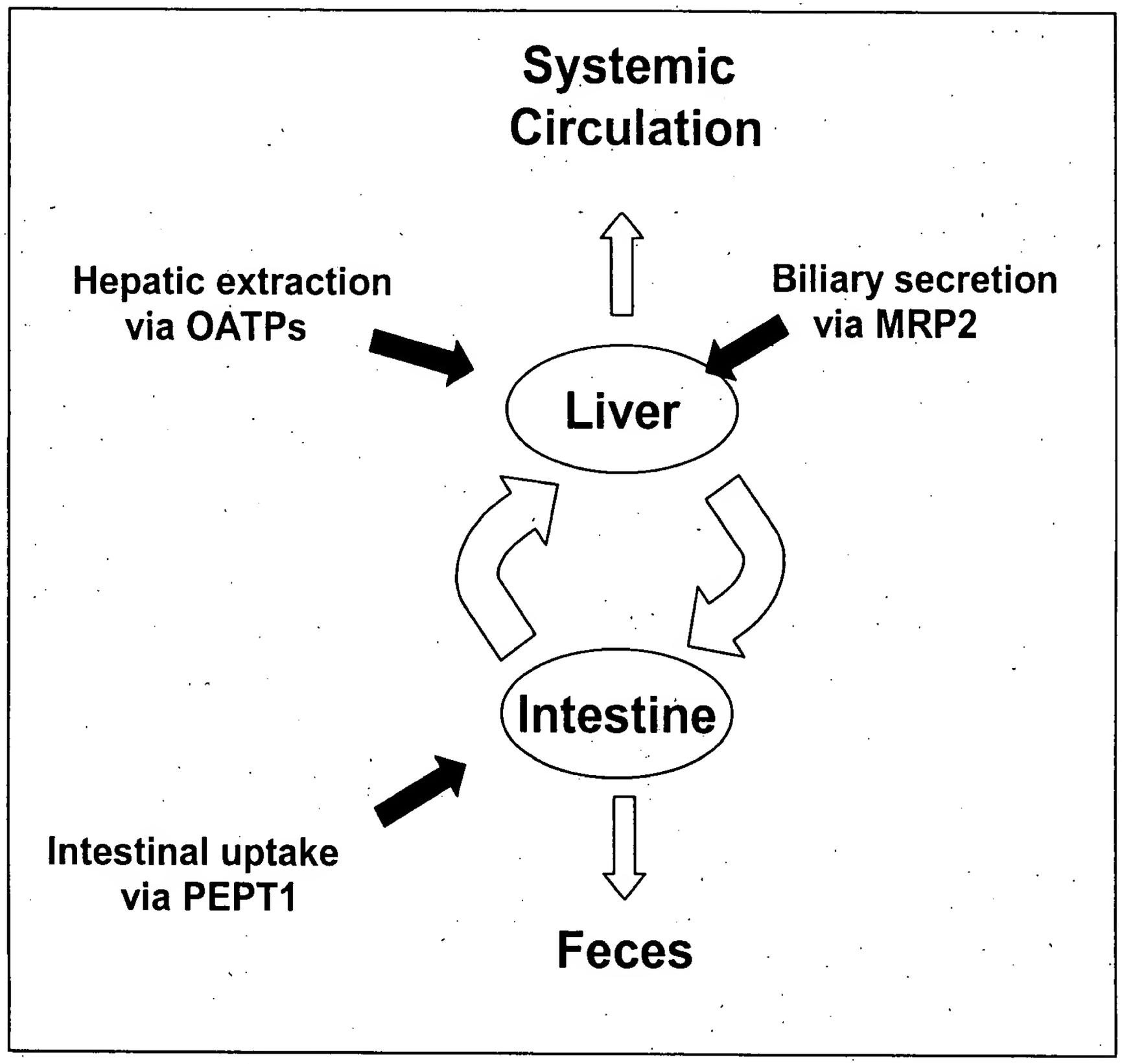
K = O , NR7 , CR8R9 ; $S(O)_j$ , j = 0, 1, or 2

Each of R21 to R23 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkoxy, substituted alkoxy, acyl, substituted acyl, acylamino, substituted acylamino, alklysulfinyl, substituted alkylsulfinyl, alkylsulfonyl, substituted alkylsulfonyl, alkylthio, substituted alkylthio, alkoxycarbonyl, substituted alkylthio, aryl, substituted aryl, arylalkyl, substituted arylalkyl, aryloxy, substituted aryloxy, carbamoyl, substituted carbamoyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, halo, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, heteroalkyloxy, substituted heteroalkyloxy, heteroaryloxy and substituted heteroaryloxy

Preferably R22 and R23 are independently selected from the group consisting of hydrogen, alkyl and substituted alkyl

R26 and R27 are independently selected from the group consisting of halo and lower alkyl (including branched alkyl)

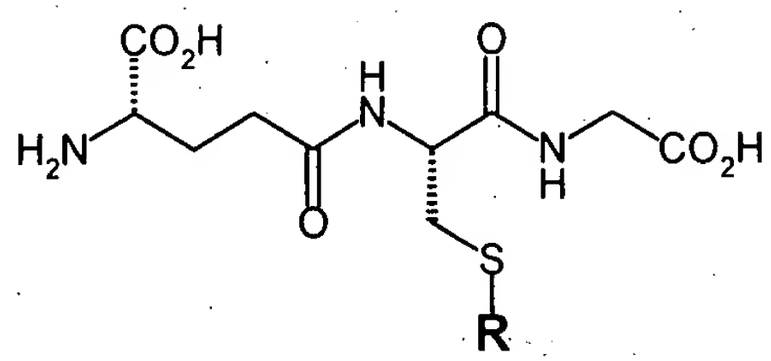
# Enterohepatic Circulation Mediated by Intestinal Peptide and Hepatic Anion Transporters



# Figure 9

## Enterohepatic Recirculating Prodrugs Based On Glutathione Mimetics

**Glutathione Conjugate**

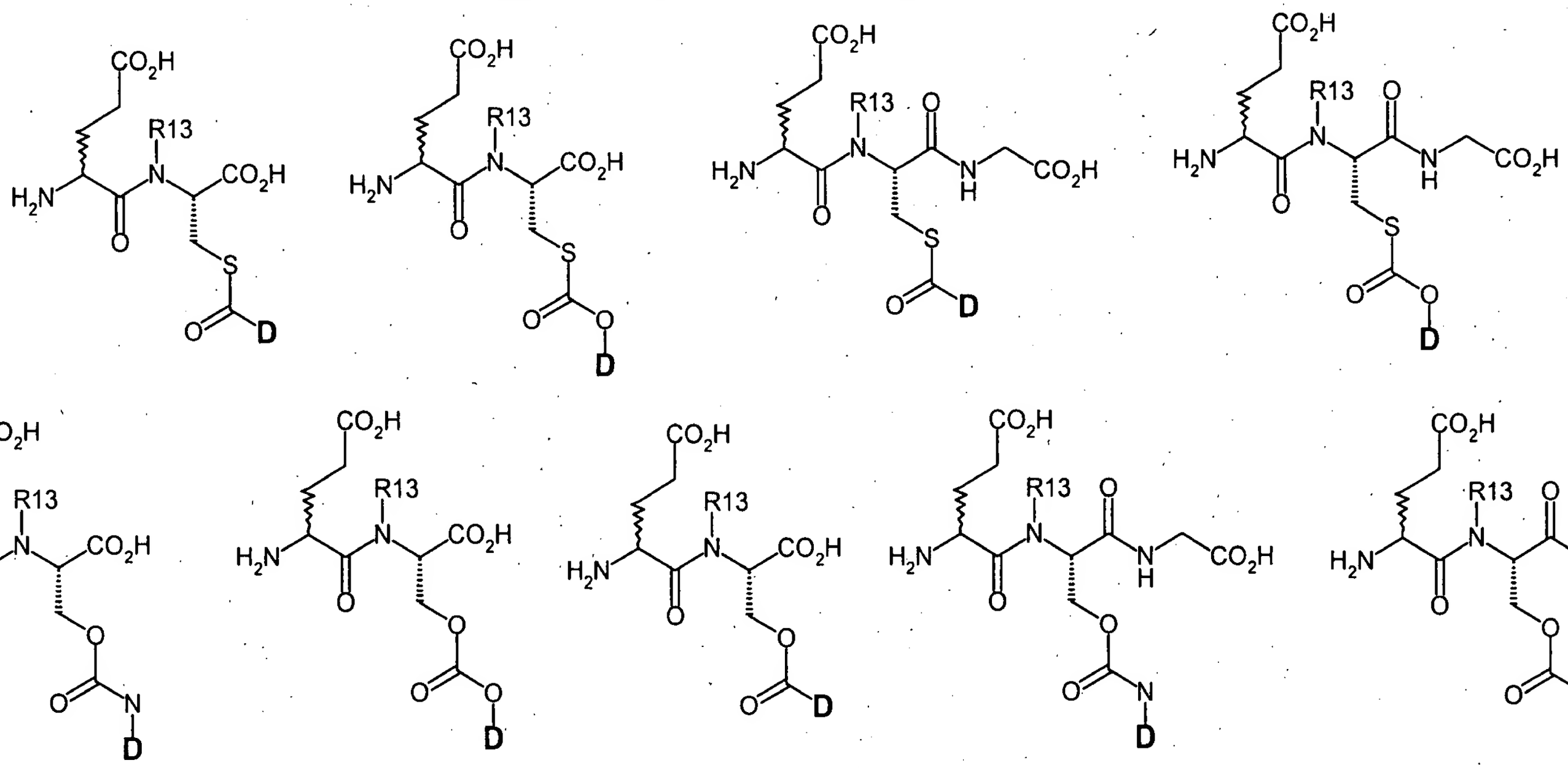


**Substrate for OATP on sinusoidal membrane of liver**

**Subtrate for MPR2 on canilicular membrane of liver**

**Not transported by PEPT1**

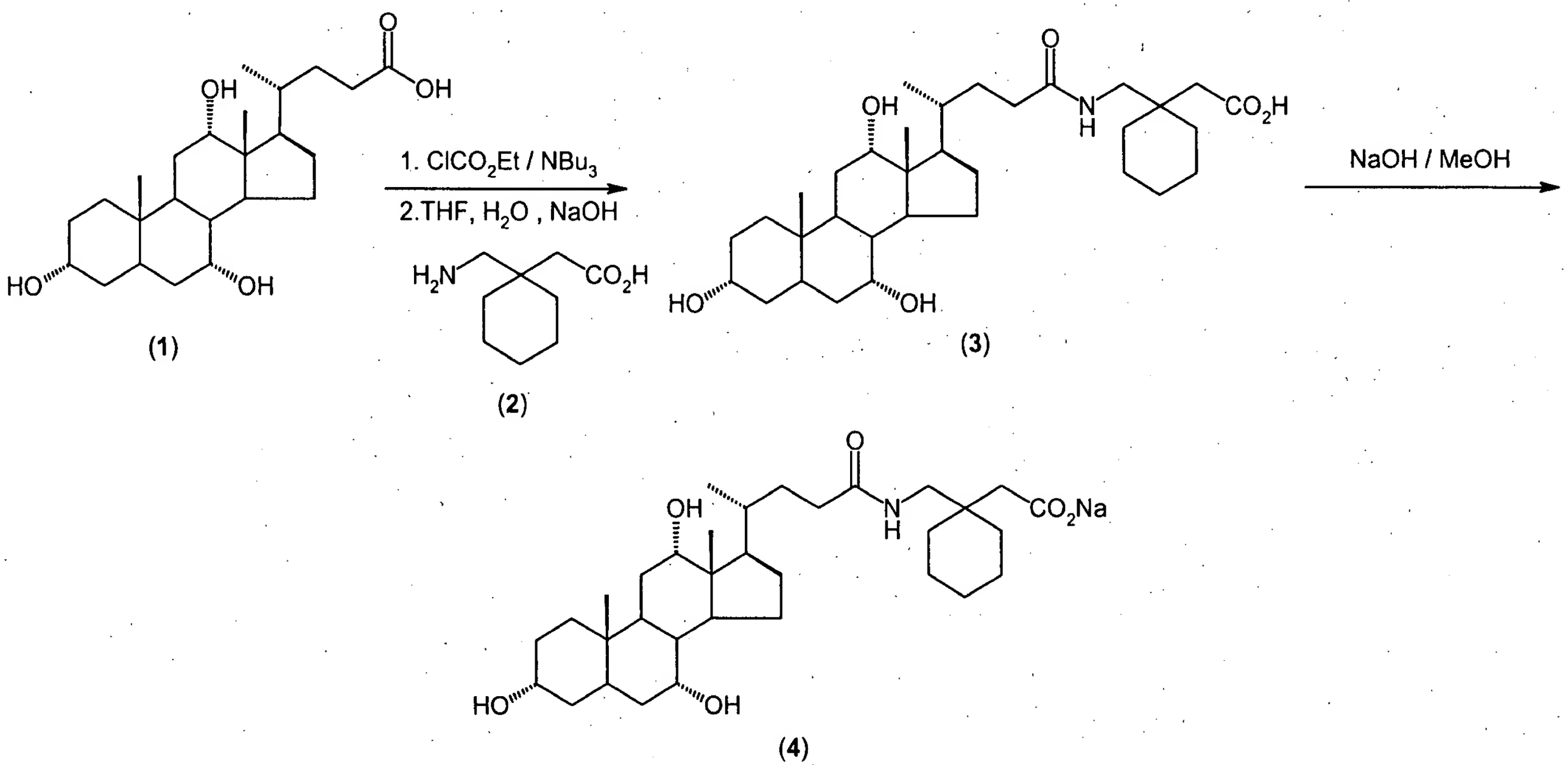
### Examples of Di- and Tripeptide Prodrugs of Hydroxyl, Amine and Carboxylic Acid-Containing Drugs Based on Glutathione-Like Motif



**R13 = H , lower alkyl**

**Use PEPT1 substrate with metabolically stable di- or tripeptide backbone to achieve intestinal absorption**

# Figure 10


OH
O
OH
HO
OH
1. ClCO2Et / NBu3
2.THF, H2O , NaOH
H2N
CO2H
(1)
(2)
O
OH
N
H
CO2H
HO
OH
(3)
NaOH / MeOH
O
OH
N
H
CO2Na
HO
OH
(4)

# Figure 11

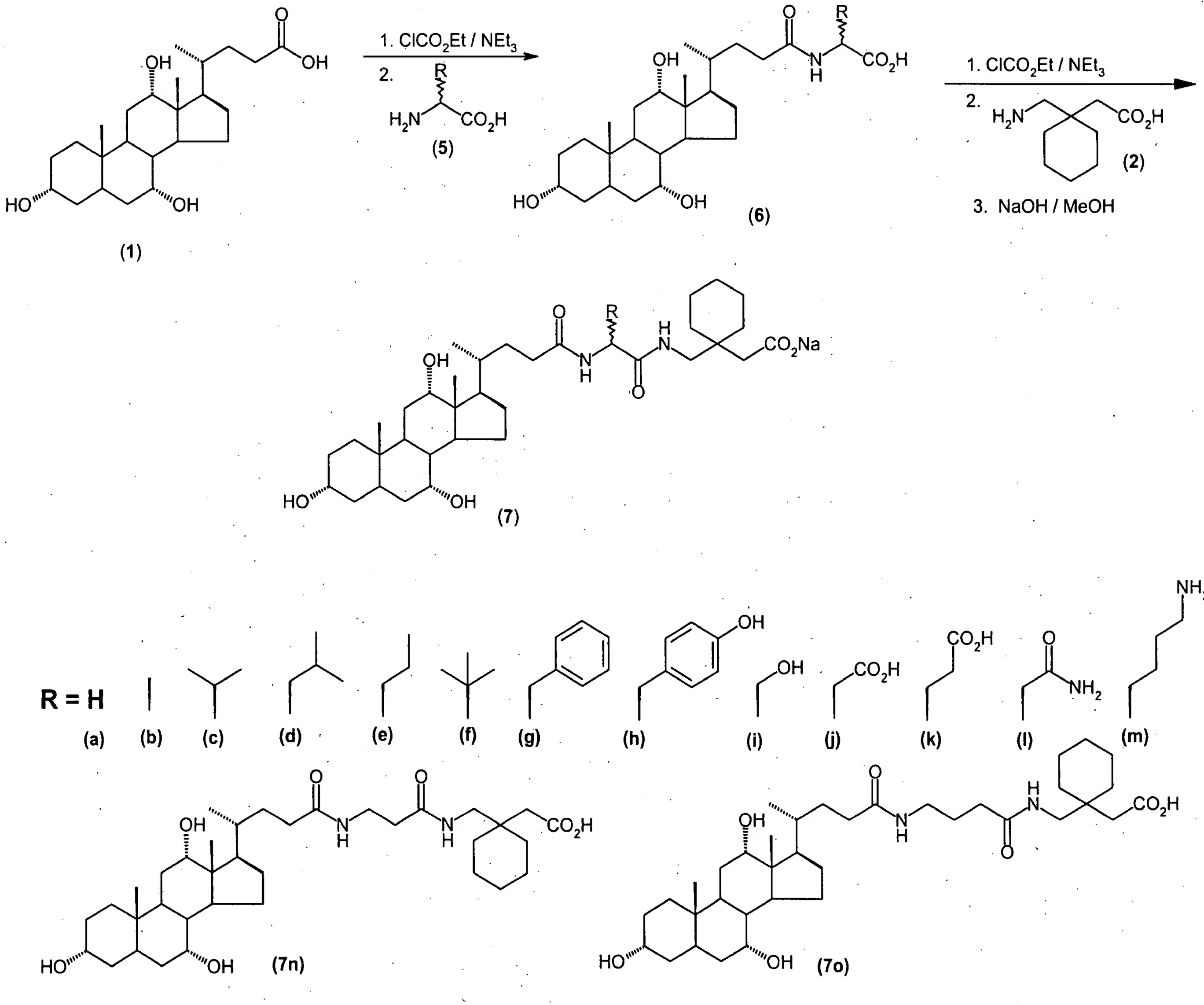
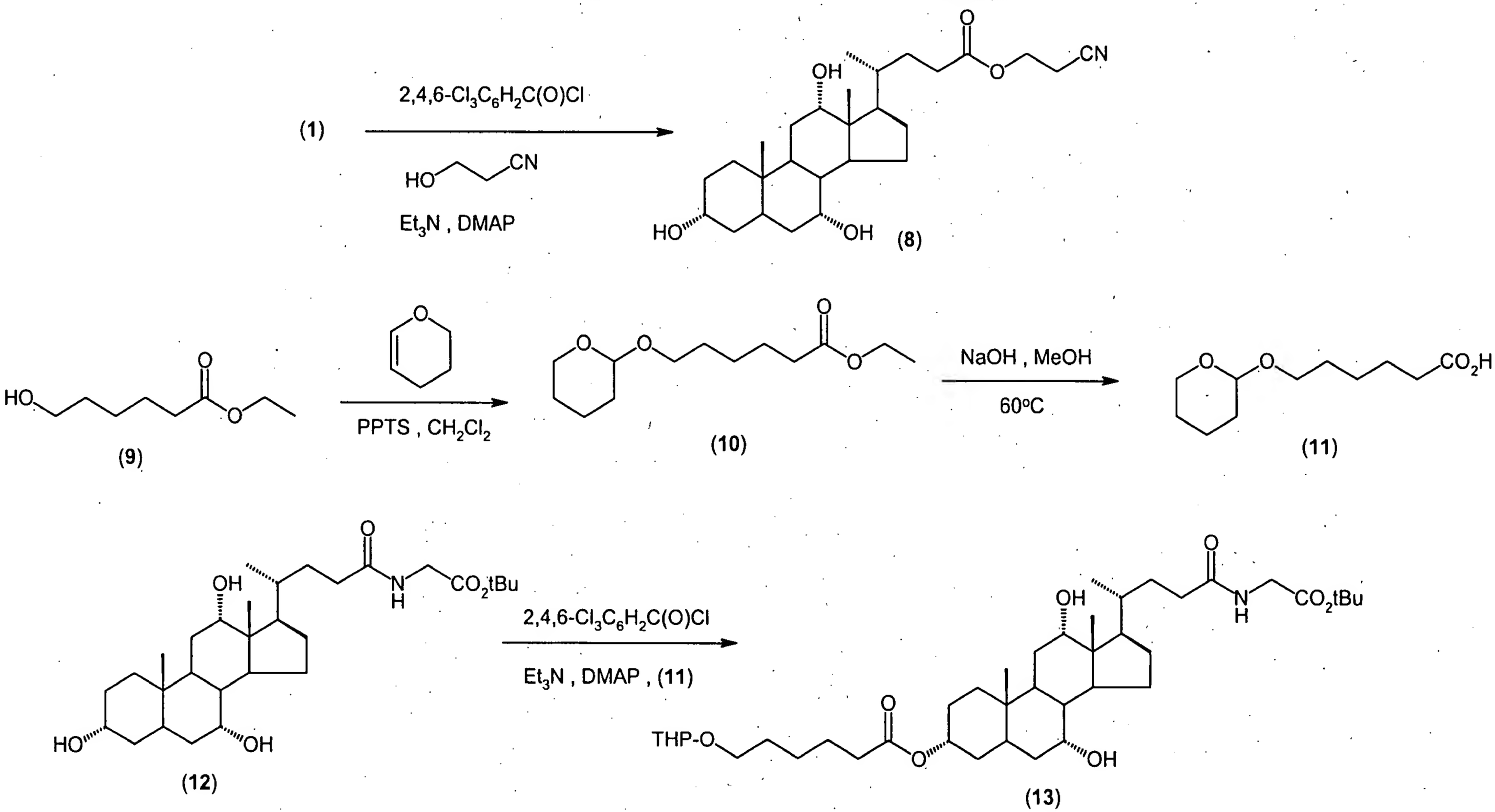
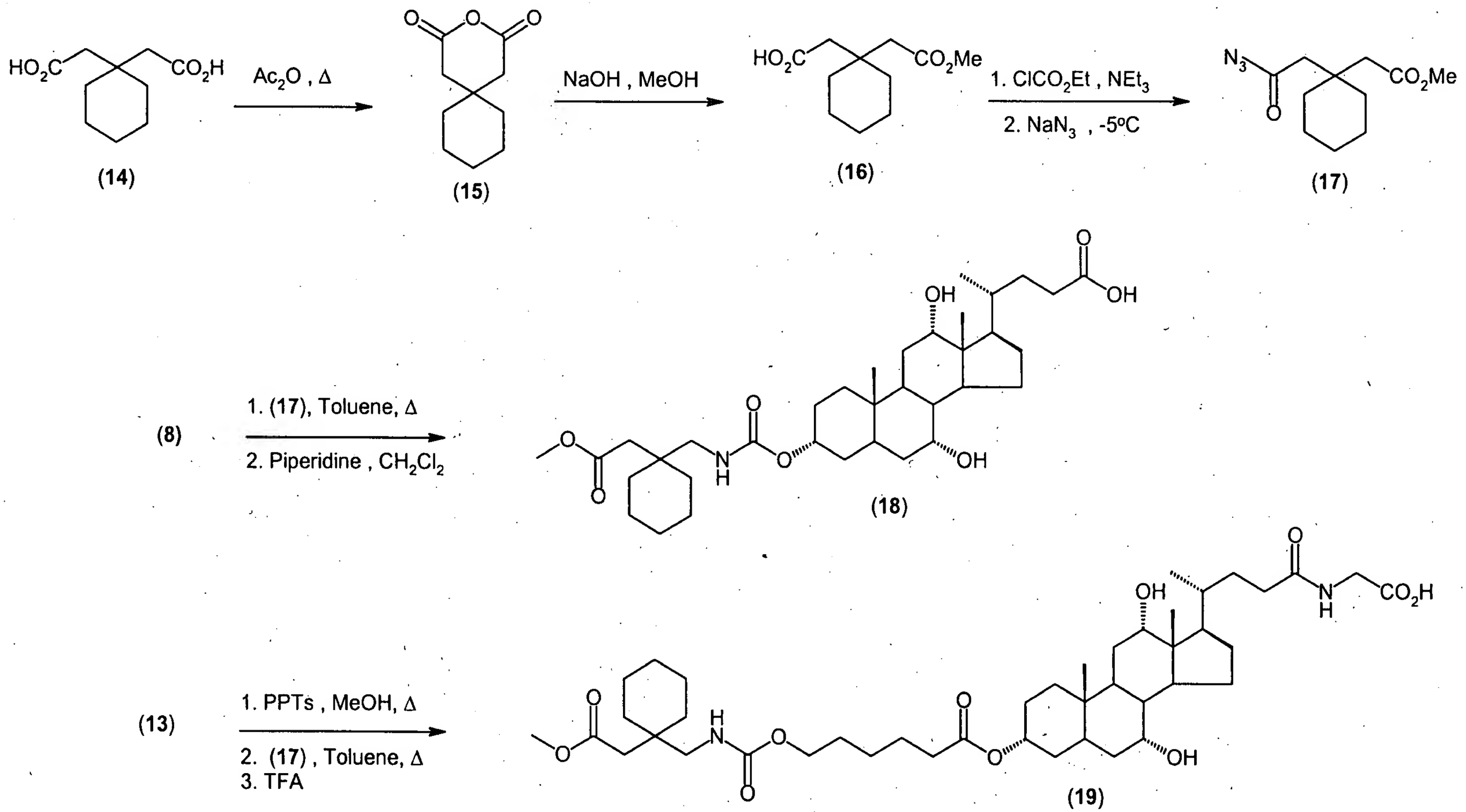

1. ClCO2Et / NEt3
2.
(5)
1. ClCO2Et / NEt3
2.
(2)
3. NaOH / MeOH
(1)
(6)
(7)
R = H
(a)
(b)
(c)
(d)
(e)
(f)
(g)
(h)
(i)
(j)
(k)
(l)
(m)
(7n)
(7o)

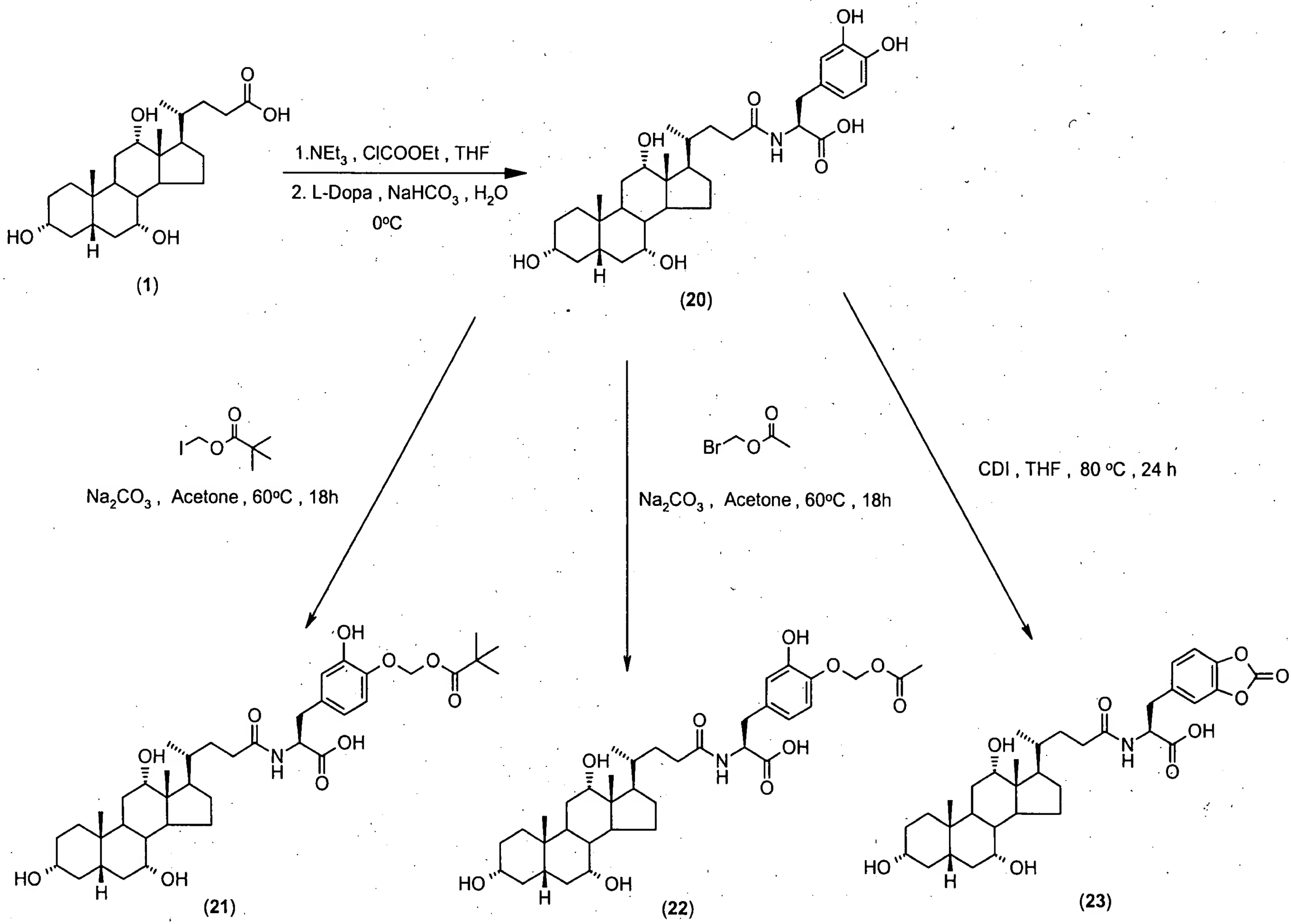
Figure 12


(1)
2,4,6-Cl3C6H2C(O)Cl
HO
CN
Et3N , DMAP
OH
HO
OH
(8)
HO
(9)
PPTS , CH2Cl2
(10)
NaOH , MeOH
60°C
CO2H
(11)
OH
HO
OH
(12)
2,4,6-Cl3C6H2C(O)Cl
Et3N , DMAP , (11)
THP-O
OH
(13)

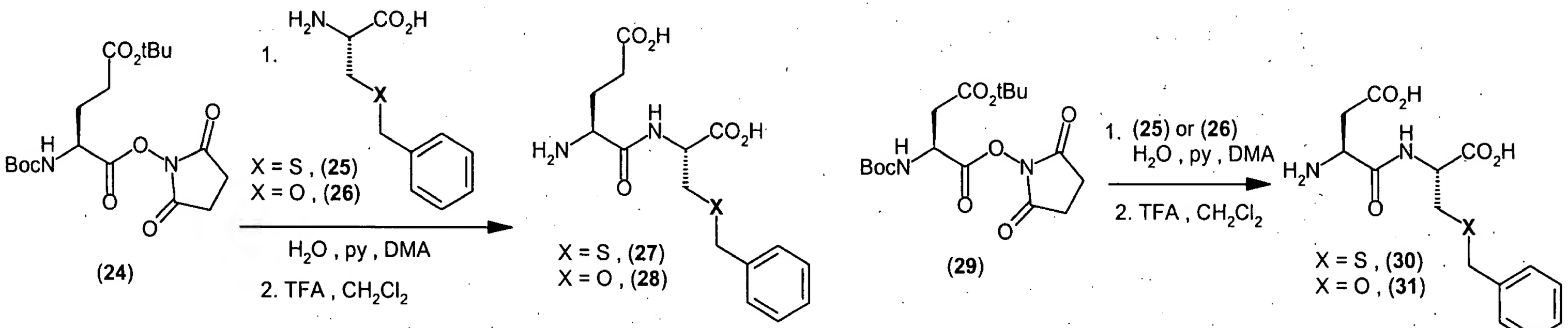
# Figure 13

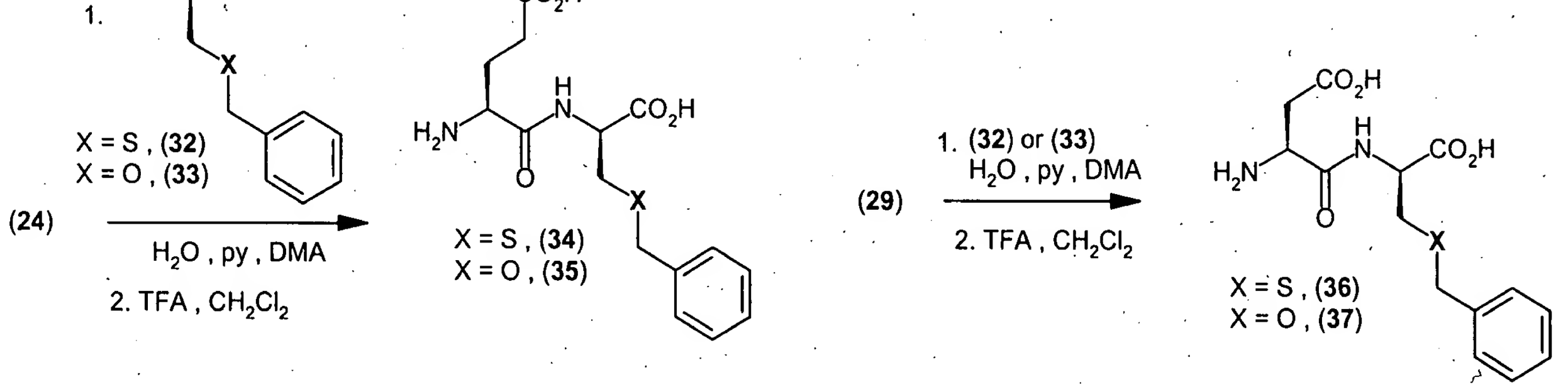

HO2C
CO2H
Ac2O , Δ
(14)
(15)
NaOH , MeOH
HO2C
CO2Me
(16)
1. ClCO2Et , NEt3
2. NaN3 , -5ºC
N3
CO2Me
(17)
(8)
1. (17), Toluene, Δ
2. Piperidine , CH2Cl2
OH
OH
OH
(18)
(13)
1. PPTs , MeOH, Δ
2. (17) , Toluene, Δ
3. TFA
OH
OH
CO2H
(19)

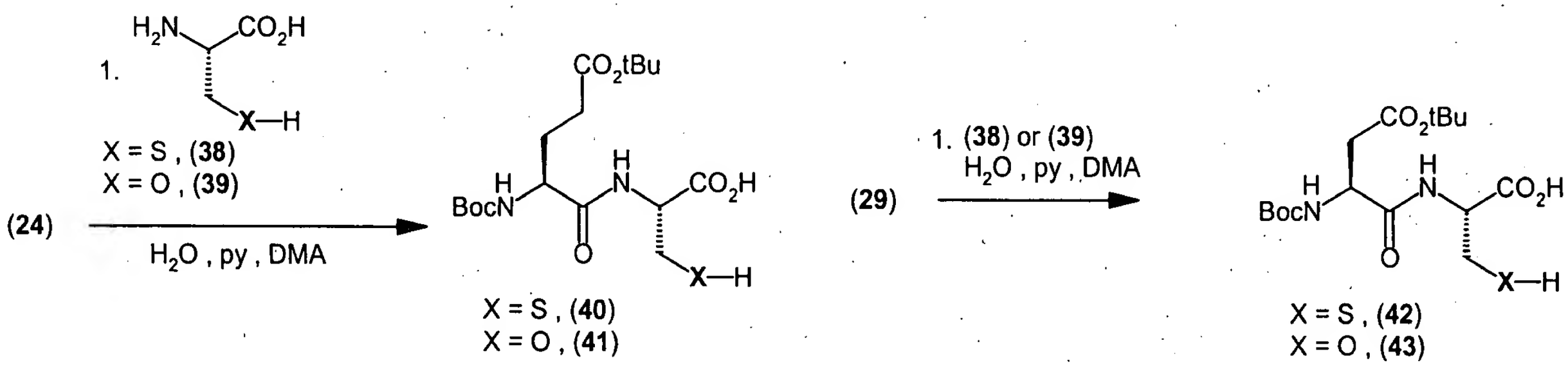
# Figure 14 - Synthesis of Cholyl-Dopa Conjugates



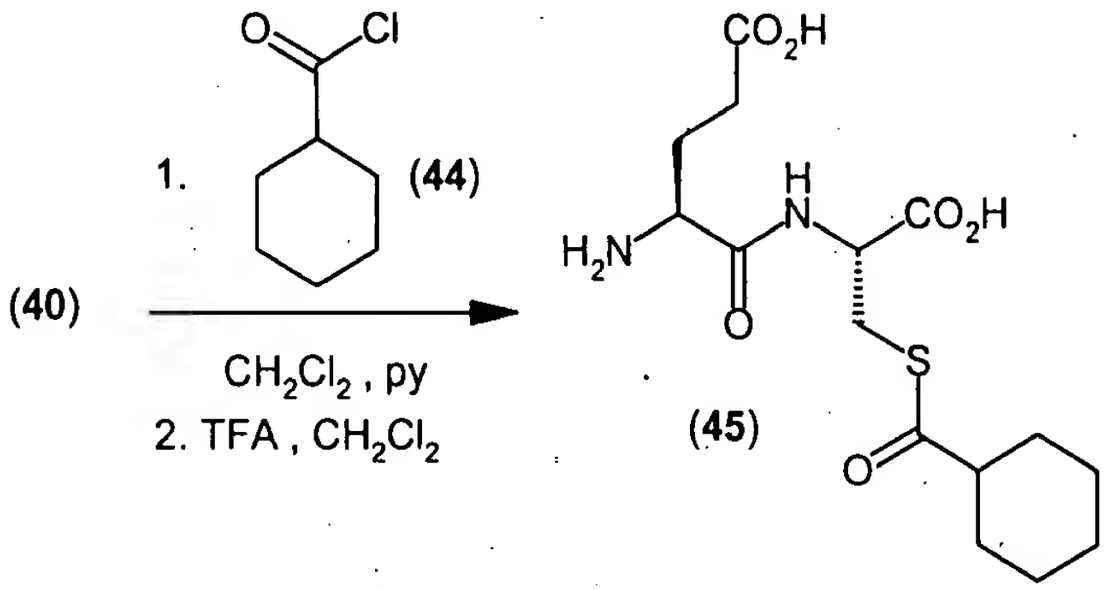
# Figure 15

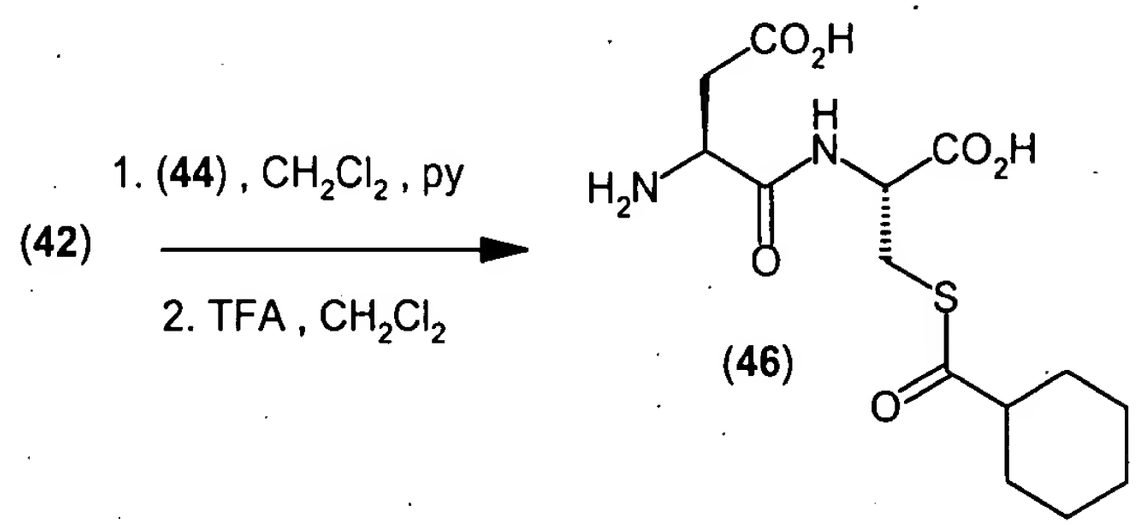

CO2tBu
H
BocN
O
N
O
O
(24)
1.
H2N
CO2H
X
X = S , (25)
X = O , (26)
H2O , py , DMA
2. TFA , CH2Cl2
CO2H
H
H2N
N
CO2H
X
X = S , (27)
X = O , (28)
CO2tBu
H
BocN
O
N
O
O
(29)
1. (25) or (26)
H2O , py , DMA
2. TFA , CH2Cl2
CO2H
H
H2N
N
CO2H
X
X = S , (30)
X = O , (31)

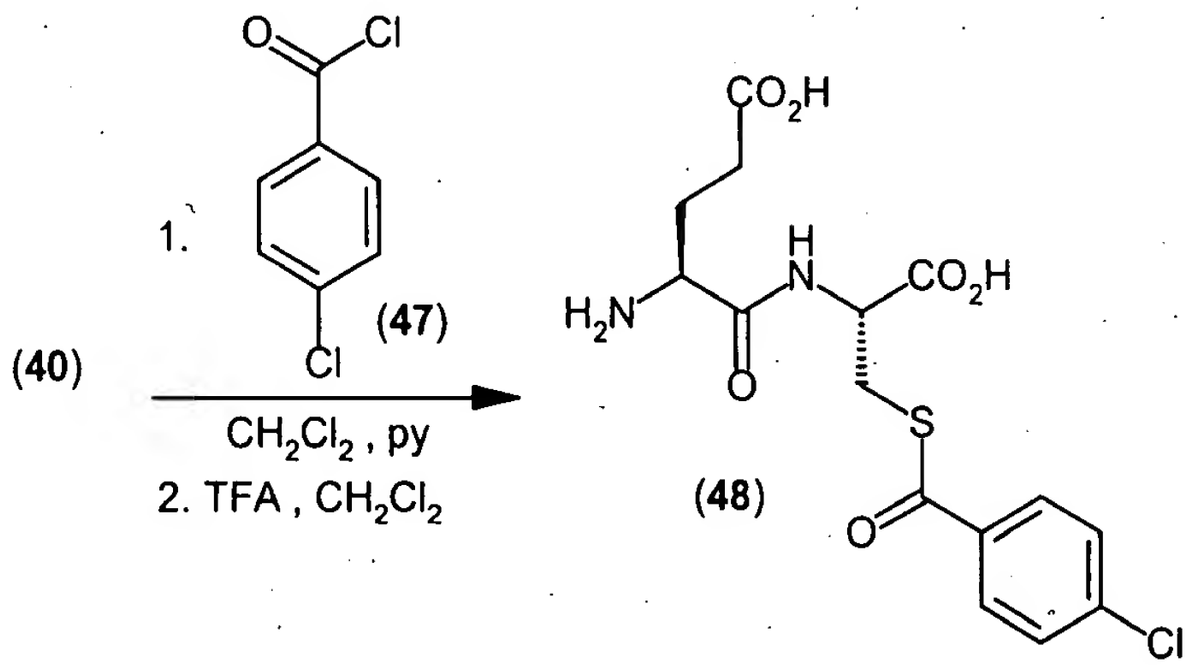

1.
H2N
CO2H
X
X = S , (32)
X = O , (33)
(24)
H2O , py , DMA
2. TFA , CH2Cl2
CO2H
H
H2N
N
CO2H
X
X = S , (34)
X = O , (35)
(29)
1. (32) or (33)
H2O , py , DMA
2. TFA , CH2Cl2
CO2H
H
H2N
N
CO2H
X
X = S , (36)
X = O , (37)

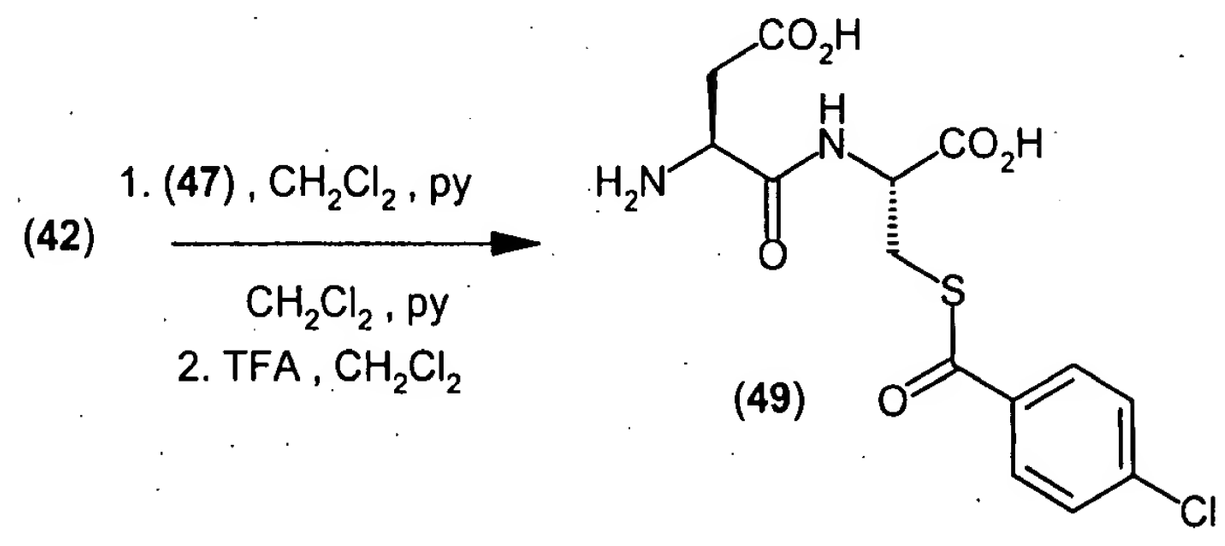

1.
H2N
CO2H
X—H
X = S , (38)
X = O , (39)
(24)
H2O , py , DMA
CO2tBu
H
BocN
H
N
CO2H
X—H
X = S , (40)
X = O , (41)
(29)
1. (38) or (39)
H2O , py , DMA
CO2tBu
H
BocN
H
N
CO2H
X—H
X = S , (42)
X = O , (43)

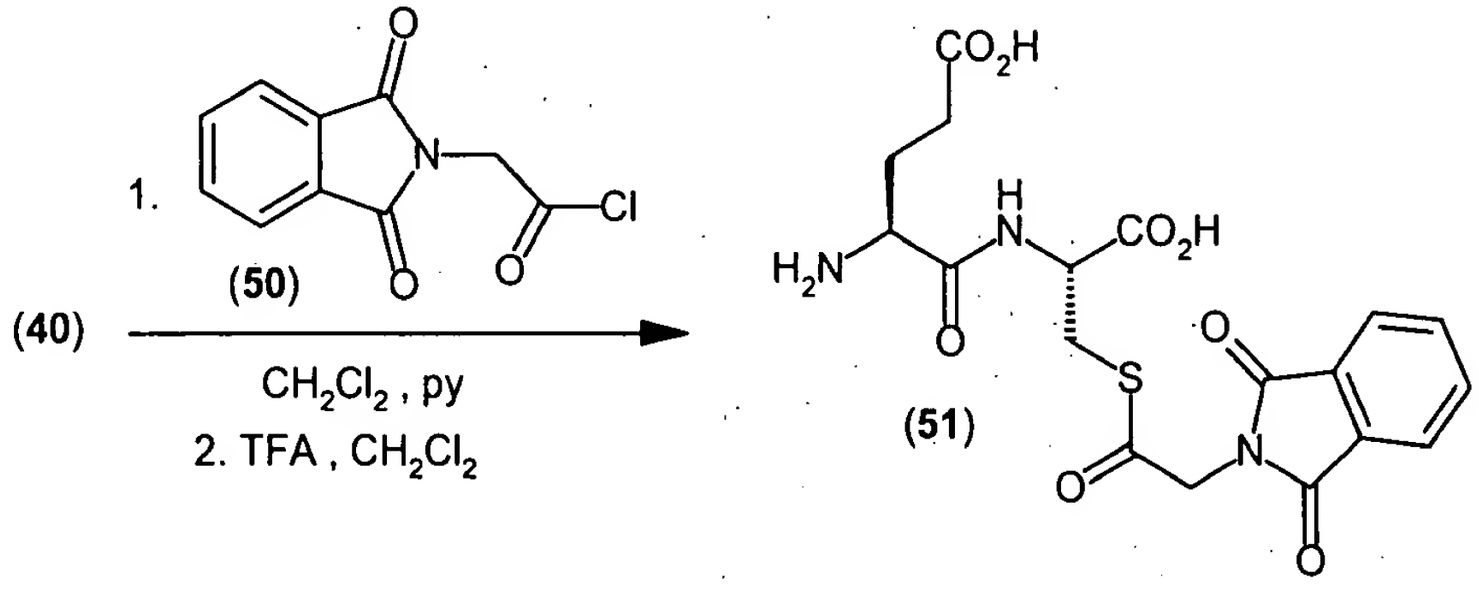
# Figure 16

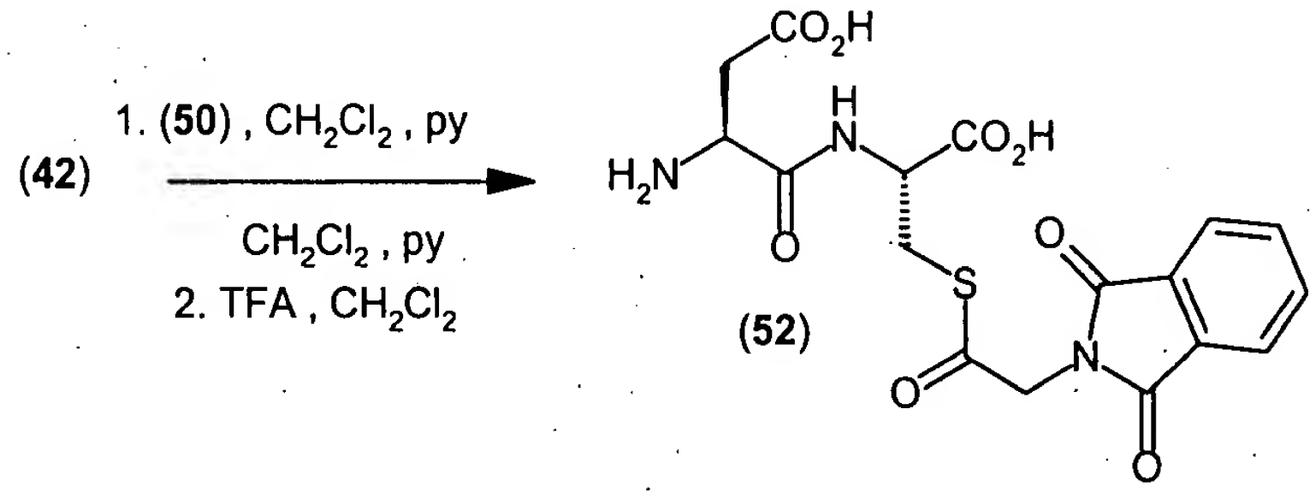

1.
(44)
(40)
$CH_2Cl_2$ , py
2. TFA , $CH_2Cl_2$
(45)


1. (44) , $CH_2Cl_2$ , py
(42)
2. TFA , $CH_2Cl_2$
(46)

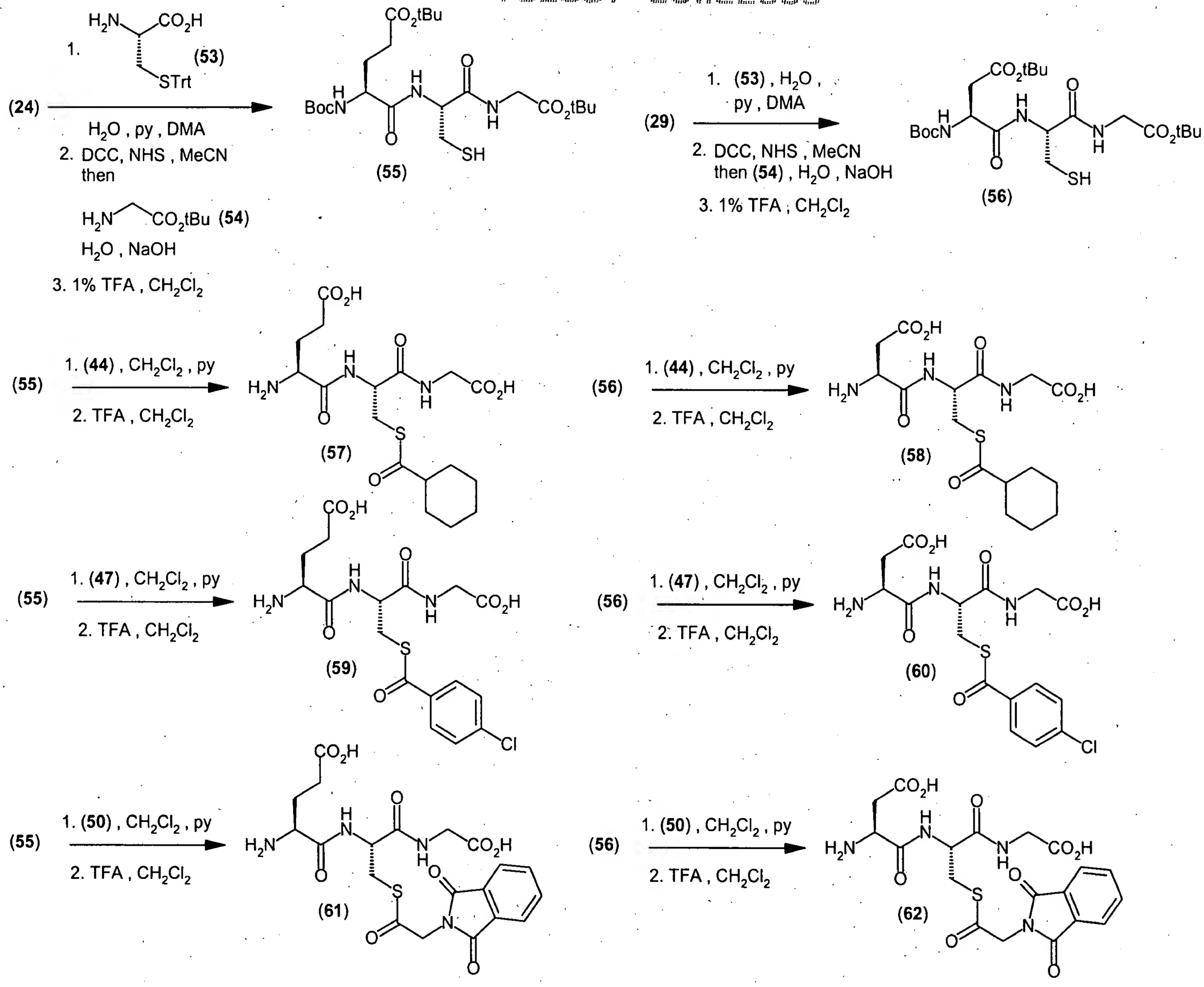

1.
(47)
(40)
$CH_2Cl_2$ , py
2. TFA , $CH_2Cl_2$
(48)


1. (47) , $CH_2Cl_2$ , py
(42)
$CH_2Cl_2$ , py
2. TFA , $CH_2Cl_2$
(49)


1.
(50)
(40)
$CH_2Cl_2$ , py
2. TFA , $CH_2Cl_2$
(51)


1. (50) , $CH_2Cl_2$ , py
(42)
$CH_2Cl_2$ , py
2. TFA , $CH_2Cl_2$
(52)

# Figure 17


1.
(53)
(24)
H2O , py , DMA
2. DCC, NHS , MeCN
then
(54)
H2O , NaOH
3. 1% TFA , CH2Cl2
(55)
(29)
1. (53) , H2O , py , DMA
2. DCC, NHS , MeCN then (54) , H2O , NaOH
3. 1% TFA ; CH2Cl2
(56)
1. (44) , CH2Cl2 , py
2. TFA , CH2Cl2
(57)
(58)
1. (47) , CH2Cl2 , py
2. TFA , CH2Cl2
(59)
(60)
1. (50) , CH2Cl2 , py
2. TFA , CH2Cl2
(61)
(62)